4164-01-P

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**[Docket No. FDA-2023-D-1275]**

# Demonstrating Bioequivalence for Type A Medicated Articles Containing Active Pharmaceutical Ingredient(s) Considered To Be Poorly Soluble in Aqueous Media, That Exhibit Little to No Systemic Bioavailability, and Are Locally Acting; Draft Guidance for Industry; Availability

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice of availability.

**SUMMARY:** The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance for industry (GFI) #279 entitled "Demonstrating Bioequivalence for Type A Medicated Articles Containing Active Pharmaceutical Ingredient(s) Considered To Be Poorly Soluble in Aqueous Media, That Exhibit Little to No Systemic Bioavailability, and Are Locally Acting; Draft Guidance for Industry." This draft guidance describes an approach to satisfy the requirements for the completion of the Bioequivalence technical section for generic Type A medicated articles (TAMAs) containing poorly soluble, locally acting, active pharmaceutical ingredients (APIs) that have little to no systemic absorption, and for which blood level studies are not considered appropriate to demonstrate product bioequivalence. The suggested approach described in this draft guidance uses a combination of *in vitro* and *in vivo* data to support a determination of bioequivalence to address the unique challenges associated with demonstrating bioequivalence of TAMAs containing poorly soluble, locally acting APIs that have little to no systemic absorption.

**DATES:** Submit either electronic or written comments on the draft guidance by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] to ensure

that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.

**ADDRESSES:** You may submit comments on any guidance at any time as follows:

*Electronic Submissions*

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

*Written/Paper Submissions*

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

*Instructions*: All submissions received must include the Docket No. FDA-2023-D-1275 for "Demonstrating Bioequivalence for Type A Medicated Articles Containing Active Pharmaceutical Ingredient(s) Considered To Be Poorly Soluble in Aqueous Media, That Exhibit Little to No Systemic Bioavailability, and Are Locally Acting." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

*Docket*: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the

prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of the guidance to the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855. Send one self-addressed adhesive label to assist that office in processing your requests. See the SUPPLEMENTARY INFORMATION section for electronic access to the draft guidance document.

**FOR FURTHER INFORMATION CONTACT:** Ian Hendricks, Center for Veterinary Medicine (HFV-172), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 240-402-0853, Ian.Hendricks@fda.hhs.gov.

**SUPPLEMENTARY INFORMATION:**

## I. Background

FDA is announcing the availability of a draft guidance for industry #279 entitled "Demonstrating Bioequivalence for Type A Medicated Articles Containing Active Pharmaceutical Ingredient(s) Considered To Be Poorly Soluble in Aqueous Media, That Exhibit Little to No Systemic Bioavailability, and Are Locally Acting." Section 512(c)(2)(A)(vi) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360b(c)(2)(A)(vi)) requires that generic new animal drug products be shown to be bioequivalent to the reference listed new animal drug (RLNAD), and section 512(n)(1)(E) of the FD&C Act requires that the sponsor provide information to show that the proposed product is bioequivalent to the RLNAD.

FDA's Center for Veterinary Medicine (CVM) has issued guidance on demonstrating bioequivalence through *in vivo* studies, and guidance on product types that may be eligible for a waiver from the requirement to perform *in vivo* bioequivalence studies, including oral solutions and other solubilized forms, parenteral solutions, some topically applied dosage forms (see Guidance for Industry #35, "Bioequivalence Guidance") and TAMAs with APIs that are

considered to be water soluble (see Guidance for Industry #171, "Demonstrating Bioequivalence for Soluble Powder Oral Dosage Form Products, and Type A Medicated Articles Manufactured from Active Pharmaceutical Ingredients Considered To Be Soluble in Aqueous Media"). However, these guidance documents do not specifically address the unique challenges associated with demonstrating bioequivalence of TAMAs containing poorly soluble, locally acting APIs. Therefore, this guidance is intended to address these unique challenges. In particular, when the TAMA is not a candidate for a waiver from the requirement to conduct *in vivo* blood level bioequivalence studies, CVM recommends via this guidance that product bioequivalence be demonstrated using alternative test approaches to those relying exclusively on animal testing. This draft guidance, when finalized, is intended to address these situations.

This level 1 draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the current thinking of FDA on "Demonstrating Bioequivalence for Type A Medicated Articles Containing Active Pharmaceutical Ingredient(s) Considered To Be Poorly Soluble in Aqueous Media, That Exhibit Little to No Systemic Bioavailability, and Are Locally Acting." It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.

## II. Paperwork Reduction Act of 1995

While this guidance contains no collection of information, it does refer to previously approved FDA collections of information. Therefore, clearance by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3521) is not required for this guidance. The previously approved collections of information are subject to review by OMB under the PRA. The collections of information in section 512(n)(1) of the FD&C Act have been approved under OMB control number 0910-0669.

## III. Electronic Access

Persons with access to the internet may obtain the draft guidance at https://www.fda.gov/animal-veterinary/guidance-regulations/guidance-industry, https://www.fda.gov/regulatory-information/search-fda-guidance-documents, or https://www.regulations.gov.

Dated: May 31, 2023.

**Lauren K. Roth,**

*Associate Commissioner for Policy.*

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